Zalcitabine

Brand Name: Hivid
Drug Class: Nucleoside Reverse Transcriptase Inhibitors

Drug Description

Zalcitabine is a synthetic pyrimidine nucleoside analogue of the naturally occurring nucleoside deoxycytidine, in which the 3'-hydroxyl group is replaced by hydrogen. Zalcitabine was formerly called 2',3'-dideoxycytidine (ddC). [1]

HIV/AIDS-Related Uses

Zalcitabine was approved by the FDA on June 19, 1992, for use in combination with other antiretroviral agents for the treatment of HIV infection in adult and pediatric patients.[2] [3] Zalcitabine is currently dosed three times daily but is being studied for twice daily dosing.[4]

Zalcitabine is not a component of recommended treatment regimens (either preferred or alternative) for antiretroviral naive patients.[5]

Pharmacology

Zalcitabine is converted intracellularly to the active metabolite, dideoxycytidine 5'-triphosphate (dd-CTP). dd-CTP inhibits the activity of the HIV reverse transcriptase (RT) both by competing with the natural substrate, deoxycytidine 5'-triphosphate (dCTP), and by incorporation into viral DNA. Because dd-CTP lacks a 3'-OH group it prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation and thus terminates viral DNA synthesis where the analogue is incorporated. ddCTP is also an inhibitor of cellular DNA polymerase-beta and mitochondrial DNA polymerase-gamma; it may be incorporated into the DNA of cells in culture.[6]

Zalcitabine is well absorbed following oral administration, but absorption shows considerable interindividual variation. Limited data suggest that absorption is similar following oral administration as a solution or tablets.[7] The mean absolute oral bioavailability of zalcitabine is greater than 80%. The time to peak plasma concentration is 1 to 2 hours.[8] Concentrations of dd-CTP are too low for quantitation following administration of therapeutic doses to humans.[9]

The absorption rate of an oral dose of zalcitabine was reduced when administered with food. This resulted in a 39% decrease in mean maximum plasma concentrations (Cmax) and a twofold increase in time to achieve maximum plasma concentrations, from a mean of 0.8 hours under fasting conditions to 1.6 hours when the drug was given with food. The extent of absorption, as reflected by the area under the plasma concentration-time curve (AUC), was decreased by 14%. The clinical relevance of this decrease is unknown.

Limited pharmacokinetic data have been reported for HIV infected pediatric patients receiving zalcitabine orally every 6 hours. The mean bioavailability of zalcitabine in these patients was 54%.

The steady-state volume of distribution following intravenous administration of a 1.5 mg dose of zalcitabine averaged 0.534 l/kg. Cerebrospinal fluid (CSF) obtained from 9 patients at 2 to 3.5 hours following 0.06 mg/kg or 0.09 mg/kg intravenous infusion showed measurable concentrations of zalcitabine, with the CSF:plasma concentration ratio ranging from 9% to 37% (mean 20%). The clinical relevance of these ratios has not been evaluated.[10]

Zalcitabine is in FDA Pregnancy Category C. There are no adequate and well-controlled studies of zalcitabine in pregnant women. It is not known whether zalcitabine crosses the human placenta; the drug does cross the placenta in rodents. It has been shown to be teratogenic in animal studies. Zalcitabine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The manufacturer advises that fertile women should not receive zalcitabine unless they are using effective contraception during therapy. If pregnancy occurs, physicians are encouraged to report such cases to the manufacturer by calling 1-800-526-6367. To monitor maternal-fetal outcomes of pregnant women exposed to antiretroviral medications, including zalcitabine, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to contact the registry by calling 1-800-258-4263 or online at

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Pharmacology (cont.)

http://www.APRegistry.com.

It is not known whether zalcitabine is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving antiretroviral medications, including zalcitabine.[11]

Zalcitabine is less than 4% bound to plasma proteins, indicating that drug interactions involving binding-site displacement are unlikely.[12]

Dideoxyuridine (ddU) is the primary metabolite of zalcitabine and accounts for less than 15% of an oral dose in both urine and feces.[13] Approximately 10% of an orally administered radiolabeled dose of zalcitabine appears in the feces as unchanged drug and ddU. Renal excretion of unchanged drug appears to be the primary route of elimination, accounting for approximately 80% of an intravenous dose and 60% of an orally administered dose within 24 hours after dosing. In adults with normal renal function, the half-life of zalcitabine ranges from 1 to 3 hours. In the presence of renal impairment (creatinine clearance less than 55 ml/min), the half-life in adults is 8.5 hours. In children ages 6 months to 13 years, the half-life is approximately 0.8 hours. The intracellular half-life of ddCTP is 2.6 to 10 hours.[14] Total clearance following an intravenous dose averaged 285 ml/min. Renal clearance averaged approximately 235 ml/min or about 80% of total clearance. In HIV infected pediatric patients receiving zalcitabine orally every 6 hours, the mean apparent systemic clearance was 150 ml/min/m2. Renal clearance exceeds glomerular filtration rate, suggesting that renal tubular secretion contributes to the elimination of zalcitabine by the kidneys. Zalcitabine does not undergo a significant degree of metabolism by the liver.[15]

Patients with renal impairment may be at a greater risk of zalcitabine toxicity due to decreased drug clearance. Dosage adjustment is recommended in these patients. Absorption of zalcitabine does not appear to be reduced in patients with diarrhea not caused by an identified pathogen.

Zalcitabine showed antiviral activity in all acute infections; however, activity was substantially less in chronically infected cells. Zalcitabine showed additive to synergistic activity with zidovudine or saquinavir in cell culture. The relationship between the in vitro susceptibility of HIV to reverse-transcriptase inhibitors and the inhibition of HIV replication in humans has not been established.

HIV isolates with reduced sensitivity to zalcitabine have been isolated within 1 year of therapy from a small number of patients treated with zalcitabine. Genetic analysis of these isolates showed point mutations in the pol gene encoding RT. Combination therapy with zalcitabine and zidovudine does not appear to prevent the emergence of zidovudine-resistant isolates.[16]

The potential for cross resistance between nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) is low because of the different enzyme targets involved.[17] The antiviral effects of NRTIs and PIs are additive or synergistic against HIV-1 in vitro.[18]

Adverse Events/Toxicity

Peripheral neuropathy is the major dose-limiting toxicity of zalcitabine and has been reported in 3% to 35% of patients taking zalcitabine. Zalcitabine-associated peripheral neuropathy is a sensorimotor neuropathy characterized initially by numbness and burning dysthesias of the distal extremities. Symptoms generally begin within the first 7 to 24 weeks of therapy. If the zalcitabine is not discontinued, symptoms progress to sharp, shooting pains or severe continuous burning and may be irreversible. Neuropathy is slowly reversible if zalcitabine is discontinued early but symptoms often progress or worsen for 3 to 4 weeks after stopping zalcitabine. Patients with more advanced HIV disease are at greater risk for zalcitabine-associated neuropathy.

Headache, fatigue, and seizure are also associated with zalcitabine therapy.[19]

Pancreatitis has been reported in 1.1% of patients

Adverse Events/Toxicity (cont.)

taking zalcitabine.[20] It begins with vague abdominal pain, nausea, and vomiting and may be fatal. Patients with a history of pancreatitis, including didanosine-associated pancreatitis, are more likely to develop zalcitabine-associated pancreatitis.

Lactic acidosis and severe hepatomegaly with steatosis have been reported rarely in patients taking zalcitabine and may be fatal. Risk factors include female gender, obesity, and long-term NRTI therapy. Abnormal liver function characterized by elevated liver enzymes has been reported in 8.9% of patients taking zalcitabine.[21] Rare cases of hepatic failure and death, possibly related to underlying hepatitis B and zalcitabine monotherapy, have been reported.

Oral ulcers and stomatitis have been reported in 3% of patients taking zalcitabine. Ulcers generally occur within 1 to 4 weeks of starting therapy and may resolve within 1 to 2 weeks. However, ulcers may also persist and progress, requiring discontinuation of zalcitabine. Abdominal pain, nausea, vomiting, diarrhea, and constipation have been reported in 1% to 3.4% of patients taking zalcitabine.

Rash, pruritis, and urticaria have also been reported. An anaphylactoid reaction was reported in one patient taking both zalcitabine and zidovudine.

Anemia may occur in 3.1% to 8.4% of patients taking zalcitabine. Leukopenia, neutropenia, and thrombocytopenia have been reported.[22]

Drug and Food Interactions

The presence of food in the gastrointestinal tract may decrease the rate and extent of oral absorption of zalcitabine. Because the clinical significance of this effect is unclear, some clinicians suggest zalcitabine be taken on an empty stomach, 1 hour before or 2 hours after a meal.[23] Other clinicians suggest that zalcitabine may be taken without regard to meals.[24] Zalcitabine should be used with extreme caution and only if clearly indicated in patients receiving other drugs that have been associated with pancreatic toxicity, such as alcohol, asparaginase, azathioprine, estrogens, furosemide, methyldopa, pentamidine, sulfonamides, sulindac, tetracyclines, thiazide diuretics, and valproic acid. Concomitant use of these drugs may increase the risk of pancreatitis.[25] Death due to fulminant pancreatitis possibly related to intravenous (IV) pentamidine and zalcitabine has been reported. The manufacturer suggests that zalcitabine be discontinued in patients who require life-sustaining treatment with other drugs known to cause pancreatitis. If IV pentamidine is required to treat Pneumocystis carinii pneumonia, treatment with zalcitabine should be interrupted.[26]

The concomitant use of zalcitabine with drugs that have the potential to cause peripheral neuropathy should be avoided where possible. Drugs that have been associated with peripheral neuropathy include chloramphenicol, cisplatin, dapsone, didanosine, disulfiram, ethionamide, glutethimide, gold, hydralazine, iodoquinol, isoniazid, lithium, metronidazole, nitrous oxide, phenytoin, ribavirin, stavudine, and vincristine.

Concomitant use of nitrofurantoin with zalcitabine may increase the risk of pancreatitis and peripheral neuropathy; if concurrent use is necessary, patients should be monitored for signs of toxicity and the dose of zalcitabine may need to be reduced.[27]

Drugs with nephrotoxic potential, such as such as amphotericin, foscarnet, and aminoglycosides, may increase the risk of developing peripheral neuropathy or other zalcitabine-associated adverse events by interfering with the renal clearance of zalcitabine and raising systemic exposure. Patients who require the use of these drugs with zalcitabine should have frequent clinical and laboratory monitoring; zalcitabine dosage should be adjusted for any significant change in renal function.

Concomitant administration of probenecid or cimetidine decreases the elimination of zalcitabine, most likely by inhibition of renal tubular secretion of zalcitabine. Patients receiving these drugs in combination with zalcitabine should be monitored for signs of toxicity and the dose of zalcitabine should be reduced if warranted.[28]

Absorption of zalcitabine is moderately reduced (approximately 25%) when coadministered with

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Drug and Food Interactions (cont.)

magnesium/aluminum-containing antacid products. It is not recommended that zalcitabine be ingested simultaneously with magnesium/aluminum-containing antacids.[29]

In vitro, lamivudine significantly inhibits zalcitabine phosphorylation in a dose-dependent manner. Concomitant use of zalcitabine and lamivudine is not recommended.[30]

In vitro studies of zalcitabine with doxorubicin, ribavirin, or dipyridamole showed potential effects on zalcitabine levels. The clinical relevance of these in vitro results is unknown.[31]

Contraindications

Zalcitabine is contraindicated in patients with clinically significant hypersensitivity to zalcitabine or any ingredient in the formulation.[32]

Clinical Trials

For information on clinical trials that involve Zalcitabine, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Zalcitabine AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[33]

Dosage Form: Film-coated tablets containing zalcitabine 0.375 mg or 0.750 mg.

The recommended dose of zalcitabine is 0.750 mg every 8 hours. For patients with impaired renal function, the recommended zalcitabine doses are as follows: for creatinine clearance 10 to 40 ml/min, 0.750 mg of zalcitabine every 12 hours; for creatinine clearance less than 10 ml/min, 0.750 mg of zalcitabine every 24 hours.[34]

Storage: Store tablets at 15 C to 30 C (59 F to 86 F) in a tightly closed bottle.[35]

Chemistry

CAS Name: Cytidine, 2',3'-dideoxy-[36]

CAS Number: 7481-89-2[37]

Molecular formula: C9-H13-N3-O3[38]

C51.18%, H6.20%, N19.89%, O22.72%[39]

Molecular weight: 211.22[40]

Melting point: 215-217 C[41]

Physical Description: White to off-white crystalline powder.[42]

Solubility: 76.4 mg/mL at 25 C in aqueous solution.[43]

Other Names

ddCyd[44]

Dideoxycytidine[45]

Ro 24-2027/000[46]

ddC[47]

NSC-606170[48]

Further Reading

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Zalcitabine

Manufacturer Information

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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